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13. ABSTRACT *(Maximum 200 words)*

Prevention of secondary brain injuries following head trauma can be accomplished most easily when intracranial pressure (ICP) is monitored. However, current measurement techniques are invasive and thus not practical in the combat environment. The Pulsed Phase Lock Loop device, which was developed and patented by consultants Drs. Yost and Cantrell, uses a unique, noninvasive ultrasonic phase comparison method to measure slight changes in cranial volume which occur with changes in ICP. Year two studies included whole body head-up and head-down tilting effects on intracranial compliance and pressure in six healthy volunteers. Skull movements on the order of μm were highly correlated with ICP variations due to cerebral arterial pulsation. The amplitudes of arterial blood pressure and those of ICP associated with one cardiac cycle were inversely correlated with the angle of tilt. Thus, postural changes alter intracranial compliance in healthy volunteers and intracranial volume-buffering capacity is reduced in head-down position. Additionally, this past year we continued our cadaveric studies with and without external compression to damper cranial pulsations due to simulated arterial pulsation. We found that waveform amplitude measured by our noninvasive device was reduced with increased external compression of the skull.

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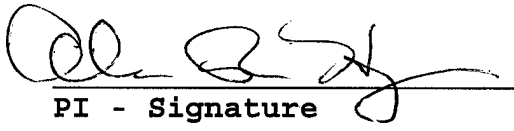

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INTRODUCTION

During this past year we accomplished all of the goals which we set forth for Year –02 on this project. First, we undertook head-up and head-down tilt studies of normal volunteers after obtaining informed, written consent. We analyzed intracranial pressure (ICP) waveforms because these waveforms contain information on intracranial compliance and cerebrovascular tonus which cannot be estimated from mean ICP (2). Our technique, the principle of which is called pulsed phase-locked loop (PPLL), is based upon detecting skull movements which occur with fluctuations in ICP. Although the skull is often assumed to be a rigid container with a constant volume, many researchers (4, 5, 7, 9, 10) have demonstrated that the skull moves on the order of a few μm in association with changes in ICP. This year's studies were designed to validate our noninvasive technique for the measurement of ICP waveforms during whole body tilt and external compression of cadaver skulls. We decided to study compression of cadaver skulls because ICP conditions could be more carefully controlled than in normal volunteers whose skin blood flow confounds data interpretation.

METHODS

The ultrasound technique we utilized to detect skull pulsation is based upon a modification of the pulsed phase-lock loop design (14), making it possible to measure slight changes in distance between an ultrasound transducer and a reflecting target. Sensitivity of the device is on the order of 0.1 μm. In the typical operation of the PPLL, the instrument transmits a 500 kHz ultrasonic tone burst through the cranium via a transducer placed on the head. The ultrasonic wave passes through the cranial cavity, reflects off the inner surface of the opposite side of the skull, and is received by the same transducer. The instrument compares the phase of emitted and received waves and alters the frequency of the next stimulus to maintain a 90° phase difference between the output of the device and the received signal. This repetition takes place at intervals of approximately 0.5 msec to 20 ms.

1. WHOLE-BODY TILT STUDY

Our first study was therefore designed to investigate whole body tilting effects on ICP dynamics, especially intracranial compliance, using our noninvasive technique. We hypothesized that head-down tilt reduces intracranial compliance due to a blood shift to the head followed by elevation of ICP.

PROCEDURE

The protocol of this study was approved by NASA Ames Human Research Institutional Review Board. Six healthy volunteers (two males and four females: age with mean±SD of 24±4 years old, height 168±10 cm, and weight 66±13 kg) participated in this study, after giving informed written consent. To minimize accumulative effects caused by tilting, the subjects were randomly tilted up or down sequentially at 60°, 30° head-up, supine (0°), and 15° head-down position for one minute at each angle.

MEASUREMENTS

Arterial blood pressure: Arterial blood pressure and heart rate were monitored with an inflatable wrap-on finger pressure cuff (Finapres Model 2300, Ohmeda, Englewood, CO). An infrared plethysmograph mounted on the inside of the pressure cuff detected changes in the arterial blood volume (8). A very fast pneumatic valve varied finger cuff pressure to oppose the initial changes in the arterial blood volume. In principle, the cuff never occluded the artery. Accordingly, the cuff pressure followed intra-arterial pressure changes continuously. A finger, a measurement point, was placed at the heart level throughout the procedure. According to previous studies, blood pressure measured with Finapres correlates well with blood pressure measured with a standard technique during postural changes (13).

Although the ultrasonic frequency is altered every 0.5 ms by the PPLL circuit, the number of the ultrasonic frequency can be transferred to a recording system 3-5 times per second. This sampling rate is not enough to analyze pulsatile components associated with a cardiac cycle. Recently, we modified a PPLL circuit so as to record pulsatile components of the cranial distance in higher sampling rates. The modified PPLL circuit integrates error signals of the phase shift from normal 90° phase difference while the ultrasonic frequency is being altered. The integrated error signal, which is obtained in the units of voltages, theoretically correlates with altered path length relatively.

Furthermore, we performed signal averaging using the QRS complex of the electrocardiogram as a trigger. A data stream recorded over 30 seconds is fragmented using the QRS complex. Then, the fragmented data are simply summed up and divided by the number of a cardiac cycle. Although the length of each fragmented data is different from data to data due to the variability of a cardiac cycle, this variability is not taken into account. By averaging data across several cardiac cycles using the QRS complex, superimposed noises which are not associated with a cardiac cycle are canceled, and waveforms associated with arterial pulsation are more clearly.

2. CADAVER SKULL COMPRESSION STUDY

In supine position, a catheter was inserted into the frontal horn of the right ventricle through a burr hole, and the other end of the catheter was connected to pressure tubing and a plastic syringe.

To correlate PPLL output with ICP directly, a fiber optic, transducer-tipped catheter was placed in the epidural space through another burr hole. The PPLL ultrasound transducer was placed on the temporal area above the ear and fixed with pressure cuff around the head to adjust the surface pressure on the transducer. Pulsatile changes in ICP were generated by infusing saline into the lateral ventricle at a frequency of 1 Hz. We recorded PPLL output while generating ICP pulsations and thereafter increased the circumferencial pressure around the head in steps of 10 mmHg (0-40 mmHg) by inflating the pressure cuff.

3. STATISTICAL ANALYSIS

Amplitudes of arterial blood pressure (ABP) and PPLL output waveforms during one cardiac cycle at each angle of tilt were calculated from the data averaged using the QRS complex. The amplitude was defined as differences between maximum and minimum values during one cardiac cycle. These amplitude data were used for statistical analysis. For statistical analysis, linear regression analysis was performed to determine the effects of tilt angles on amplitudes. Statistical significance was set to $p<0.05$.

RESULTS

1. WHOLE-BODY TILT STUDY

Figure 1 shows typical averaged waveforms of ABP and PPLL output in one subject. The ABP waveform peak does not coincide with that of PPLL output waveforms. This phase difference occurs because the distance from the heart to a finger is longer than from the heart to the head. Also, a filtering circuit incorporated in the PPLL circuitry causes a phase delay. The phase delay does not affect waveform analysis in the present study because we focused on the amplitude of each waveform.

Linear regression analysis revealed the amplitude of arterial blood pressure was not changed significantly as a function of the tilt angle ($r=0.188$, $p=0.378$; Figure 2). However, the amplitude of PPLL output significantly decreased as the angle of tilt was lowered ($r=0.535$, $p=0.007$; Figure 3). The PPLL output waveforms, which represent ICP pulsations, are primarily generated by arterial blood pressure waveforms (1, 3), although venous pressure pulsation also has some effect on ICP pulsation. An increased amplitude of the arterial blood pressure could raise PPLL output amplitude, even if intracranial compliance remained constant. As shown in Figure 3, overall results of the arterial blood pressure did not show significant changes as a function of the tilt angle. It is, however, possible that the observed change in the PPLL output at each angle of tilt was affected by arterial blood pressure.

There are two steps in the transmission of arterial blood pressure pulsation to ICP pulsation. In the first step, arterial pressure pulsation (ΔABP) causes arterial volume pulsation (ΔABV). Arterial volume increases when arterial pressure increases, and arterial volume decreases when arterial pressure decreases. In the second step, arterial volume pulsation (ΔABV) generates ICP pulsation (ΔICP). Because the intracranial space is surrounded by a relatively rigid skull, an increase in arterial volume causes an increase in ICP pulsation, and a decrease in arterial volume causes a decrease in ICP pulsation.

Generally, compliance is defined as a ratio of change in volume over the corresponding change in pressure. Therefore, compliance of the artery (C_{artery}) and intracranial space ($C_{intracranial}$) are expressed as:

$$C_{artery} = \frac{\Delta ABV}{\Delta ABP} \quad .....(1) \qquad C_{intracranial} = \frac{\Delta ABV}{\Delta ICP} \quad .....(2)$$

From the equations (1) and (2), we obtain

$$\frac{C_{intracranial}}{C_{artery}} = \frac{\Delta ABP}{\Delta ICP} \quad \therefore C_{intracranial} = C_{artery} \Big/ \frac{\Delta ICP}{\Delta ABP} \quad .....(3)$$

Consequently, we calculated ratios of pulsation amplitudes for PPLL output over arterial blood pressure, which may be more directly associated with intracranial pressure compliance. The ratios of pulsation amplitudes for PPLL output over arterial blood pressure significantly decreased as the angle of tilt was lowered ($r=0.409$, $p=0.047$; Figure 4).

2. CADAVER SKULL COMPRESSION STUDY

The PPLL output closely followed the pulsatile component of ICP. The ratio of PPLL amplitude significantly decreased along with increased external compression around the head (Figure 5).

$y=-1.0\cdot10^{-5}x+0.0008$, $R^2=0.87(p=0.020)$

where x=circumferencial compression (mmHg) and y=ratio of PPLL amplitude to ICP amplitude (voltage/mmHg).

DISCUSSION

The ultrasonic technique (PPLL) utilized in this study was originally developed by Yost and Cantrell at NASA Langley Research Center, and has been refined in collaboration with Space Physiology Lab at NASA Ames Research Center. PPLL outputs theoretically represent skull movements, namely cranial diameter pulsation. According to our previous cadaver study (11), where ICP pulsation is manually generated, the amplitude of cranial diameter pulsation at each pulsatile cycle is linearly correlated with ICP pulsation amplitude. Additionally, a preliminary clinical study at Stanford Medical Center in patients whose ICP was monitored by the standard

invasive technique showed good correlation between the invasive and noninvasive ICP measurement techniques during a short period (10-15 minutes)(12). Thus, our technique provides reliable data in terms of the pulsatile components of ICP when measurements are conducted during relatively short periods such as in the present study. Because our technique is very sensitive to distance changes, further studies are necessary to apply this technique for monitoring ICP over longer time periods.

In the present study, a concern may be raised that postural changes caused erroneous variability and false-positive changes in the PPLL amplitude. However, we believe that effects of such motion artifacts were cancelled out by randomizing the order of tilt angles. Accordingly, we conclude that the observed changes in the amplitudes of the PPLL output represent those in the amplitudes of ICP pulsation.

Because the intracranial space is surrounded with a relatively rigid skull, the relationship between intracranial arterial volume and pressure and intracranial extravascular volume and pressure are both exponential. This non-linear relationship between intracranial volume and pressure originally developed by Marmarou and co-workers (6) is depicted in Figure 6. As defined in the equation (2), $C_{intracranial}$ is an inverse of the slope in the pressure-volume curve. Thus, a decrease in $C_{intracranial}$ indicates that a stable point shifts from the point #1 to #2 when a subject is tilted down. The present study may be the first report to suggest that postural changes alter intracranial compliance and pressure in normal healthy subjects.

CONCLUSIONS

Our noninvasive ultrasonic technique reveals that whole-body, head-down tilting decreases intracranial compliance and increases intracranial pressure in normal healthy volunteers. We also found that intracranial volume-buffering capacity is reduced in head-down position. Our cadaver skull compression results document that we are measuring pulsatile waveforms of skull movements as opposed to arterial waveforms within the skin or other extraneous artifactual phenomena.

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1. Ueno T, RE Ballard, LM Shuer, JH Cantrell, WT Yost, AR Hargens. Noninvasive measurement of pulsatile intracranial pressures using ultrasound. Acta Neurochirurgica (Suppl) 71: 66-69, 1998

2. Ueno T, RE Ballard, LM Shuer, JH Cantrell, WT Yost, and AR Hargens. Postural effects on intracranial pressure as assessed noninvasively. FASEB Journal 12 (5): A958 (5550), 1998.

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Adnan Cutuk, B.S.
Gita Murthy, M.S.
Karen Hutchinson, A.A.

FIGURE LEGENDS

Figure 1. Typical waveforms of arterial blood pressure and PPLL output are shown as solid and dash lines, respectively. Because arterial blood pressure is measured at finger, a phase difference exists between the two waveforms.

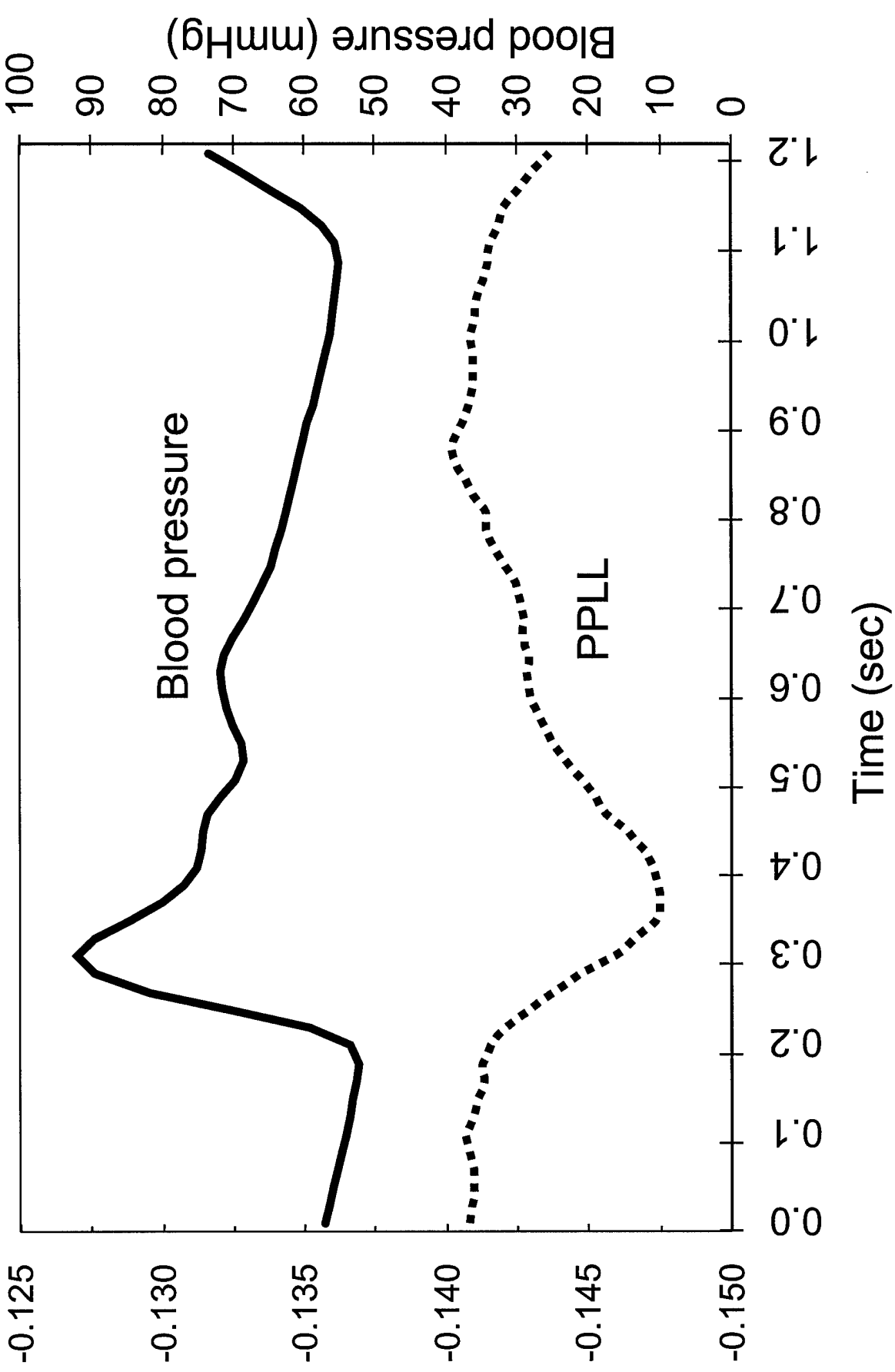
Figure 2. Amplitude changes of arterial blood pressure pulsation during whole body tilting. Small symbols represent individual data, and large squares represent mean values in six subjects. Vertical bars represent standard errors of the mean.

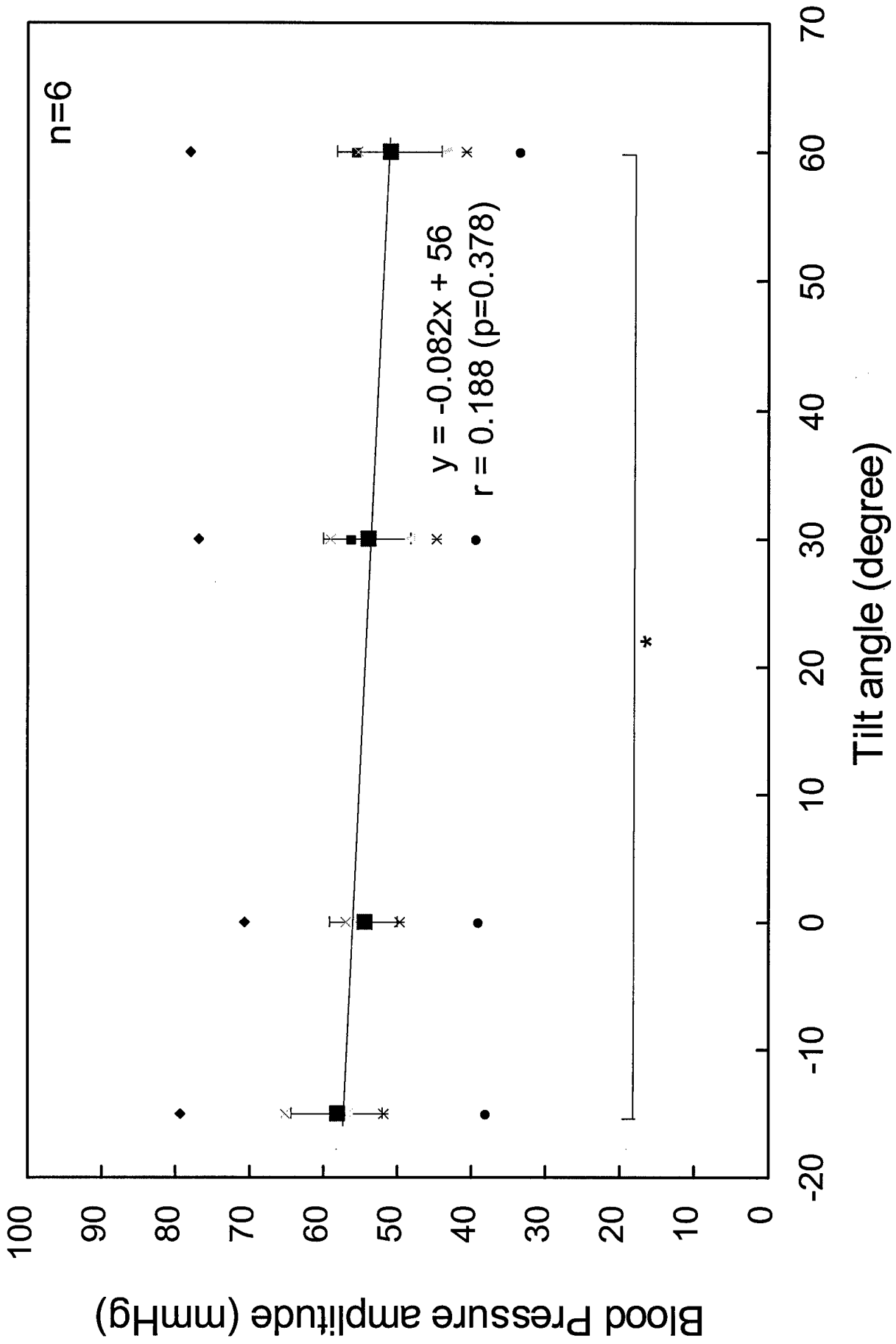
Figure 3. Amplitude changes of ICP pulsation (PPLL output) during whole body tilting. Small symbols represent individual data, and large squares represent mean values in six subjects. Vertical bars represent standard errors of the mean.

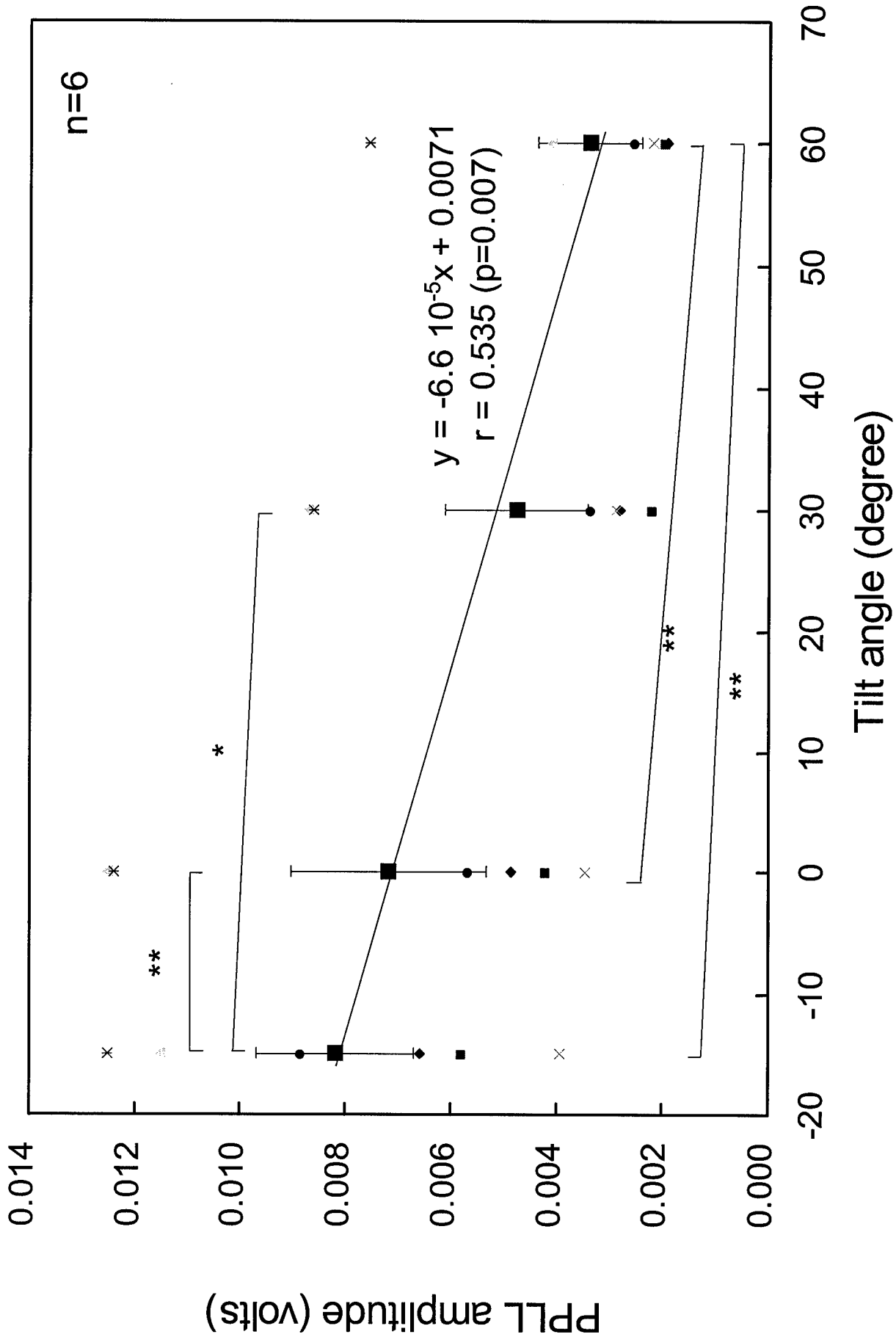
Figure 4. Altered ratios of the ICP amplitudes to the arterial pressure amplitudes during whole body tilting. Small symbols represent individual data, and large squares represent mean values in six subjects. Vertical bars represent standard errors of the mean.

Figure 5. External compression of cadaver skull reduces PPLL waveform amplitude, indicating that our noninvasive ICP technique detects pulsatile movements of bone and not skin vasculature.

Figure 6. Characteristics of the relationship between intracranial pressure and volume as originally described by Marmarou and co-workers (6). The horizontal axis represents volume of all intracranial components (brain tissue, blood, and cerebrospinal fluid). The vertical axis represents ICP.


Blood pressure (mmHg)
100
90
80
70
60
50
40
30
20
10
0
PPLL output (volts)
-0.125
-0.130
-0.135
-0.140
-0.145
-0.150
Time (sec)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
Blood pressure
PPLL


n=6
y = -0.082x + 56
r = 0.188 (p=0.378)
*
Blood Pressure amplitude (mmHg)
Tilt angle (degree)
100
90
80
70
60
50
40
30
20
10
0
-20
-10
0
10
20
30
40
50
60
70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r = 0.535 (p=0.007)
**
*
**
**
PPLL amplitude (volts)
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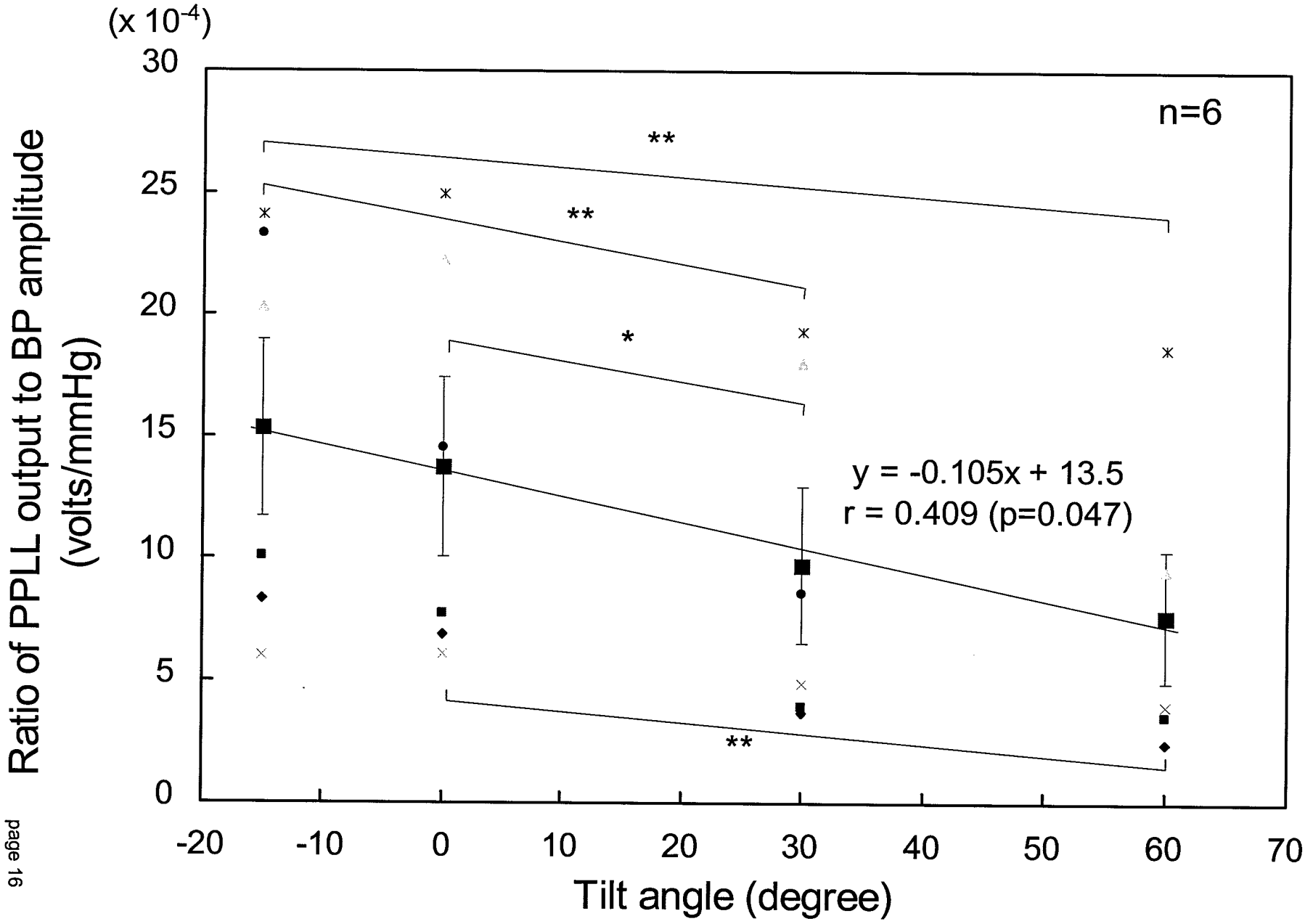
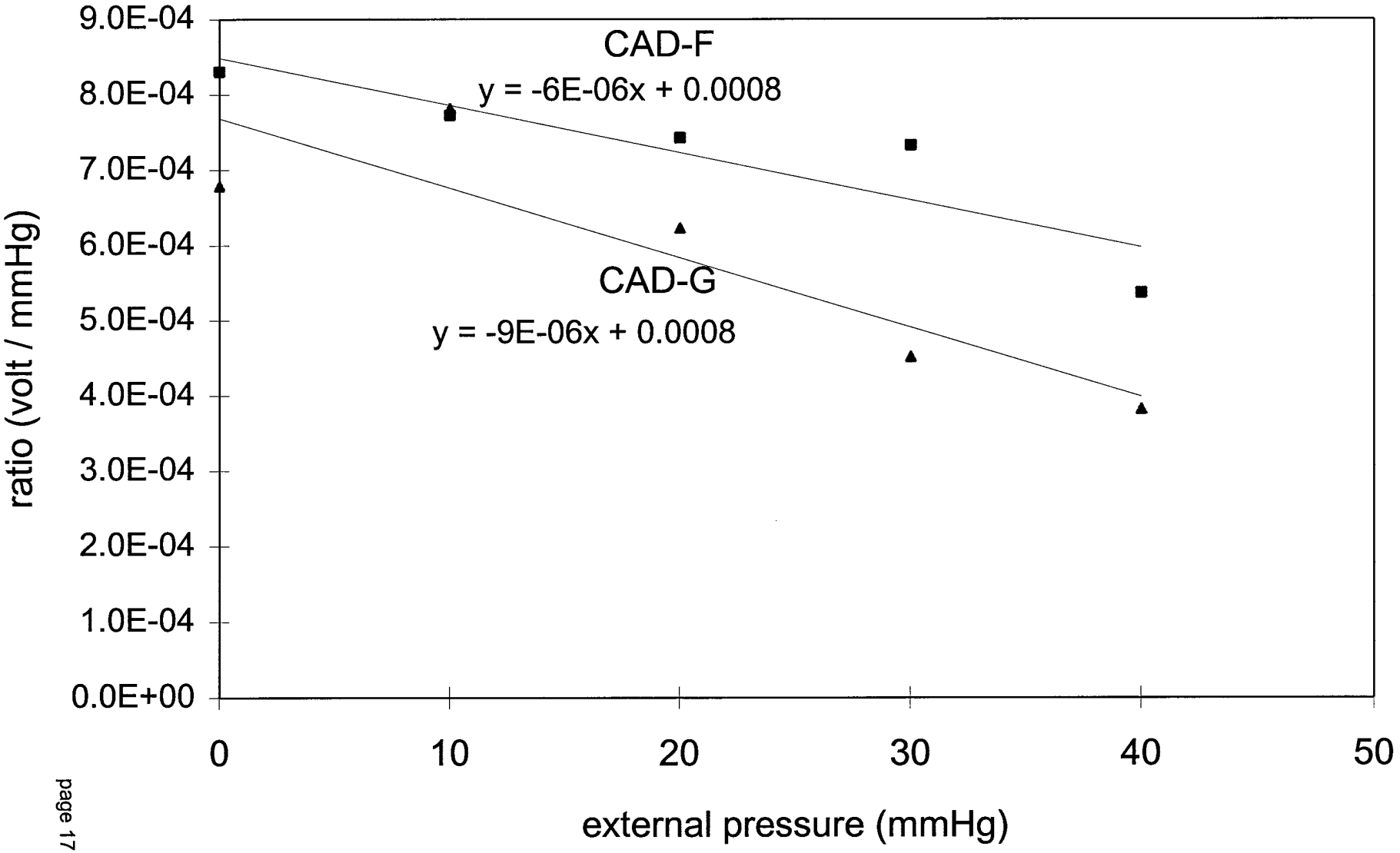
0.012
0.010
0.008
0.006
0.004
0.002
0.000
-20
-10
0
10
20
30
40
50
60
70
Tilt angle (degree)


(x 10-4)
30
25
20
15
10
5
0
Ratio of PPLL output to BP amplitude (volts/mmHg)
n=6
**
**
*
**
y = -0.105x + 13.5
r = 0.409 (p=0.047)
-20
-10
0
10
20
30
40
50
60
70
Tilt angle (degree)


CAD-F
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CAD-G
y = -9E-06x + 0.0008
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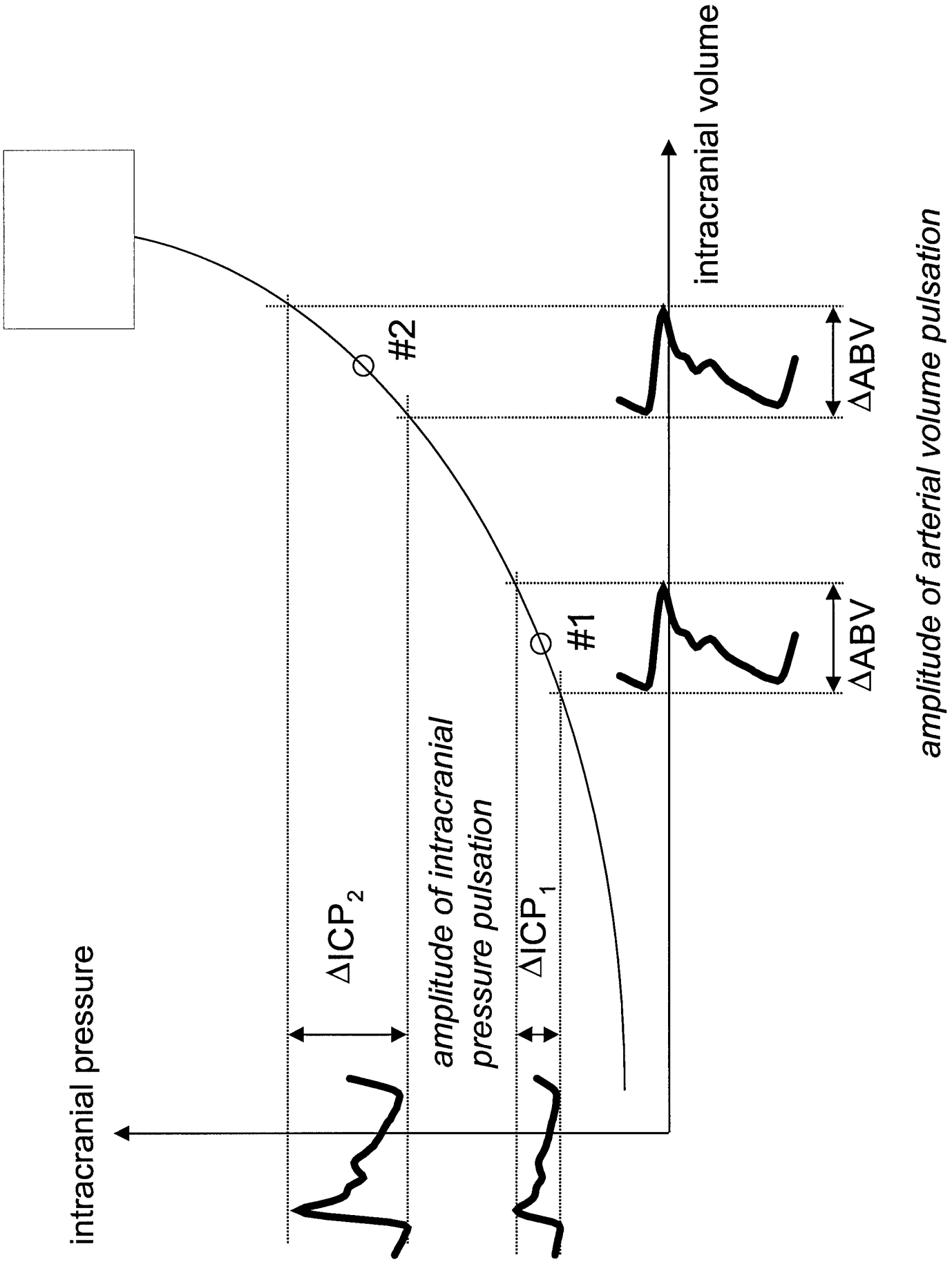
8.0E-04
7.0E-04
6.0E-04
5.0E-04
4.0E-04
3.0E-04
2.0E-04
1.0E-04
0.0E+00
ratio (volt / mmHg)
0
10
20
30
40
50
external pressure (mmHg)


intracranial pressure
intracranial volume
ΔICP2
ΔICP1
amplitude of intracranial pressure pulsation
#2
#1
ΔABV
ΔABV
amplitude of arterial volume pulsation

Acta Neurochir (1998) [Suppl] 71: 66–69

Noninvasive Measurement of Pulsatile Intracranial Pressure Using Ultrasound

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Summary

The present study was designed to validate our noninvasive ultrasonic technique (pulse phase locked loop: PPLL) for measuring intracranial pressure (ICP) waveforms. The technique is based upon detecting skull movements which are known to occur in conjunction with altered intracranial pressure. In bench model studies, PPLL output was highly correlated with changes in the distance between a transducer and a reflecting target ($R^2 = 0.977$). In cadaver studies, transcranial distance was measured while pulsations of ICP (amplitudes of zero to 10 mm Hg) were generated by rhythmic injections of saline. Frequency analyses (fast Fourier transformation) clearly demonstrate the correspondence between the PPLL output and ICP pulse cycles. Although theoretically there is a slight possibility that changes in the PPLL output are caused by changes in the ultrasonic velocity of brain tissue, the decreased amplitudes of the PPLL output as the external compression of the head was increased indicates that the PPLL output represents substantial skull movement associated with altered ICP. In conclusion, the ultrasound device has sufficient sensitivity to detect transcranial pulsations which occur in association with the cardiac cycle. Our technique makes it possible to analyze ICP waveforms noninvasively and will be helpful for understanding intracranial compliance and cerebrovascular circulation.

Keywords: Cerebrovascular circulation; intracranial pressure; noninvasive measurement.

Introduction

Elevated intracranial pressure (ICP) is used as a sign of neurological deterioration in the management of patients with head trauma, cerebrovascular diseases, and brain tumors [6]. Conventional methods for ICP monitoring require surgical procedures which are accompanied by increased risk of infection. For this reason, candidates for ICP monitoring are currently only patients with severe neurological conditions. A noninvasive technique could make it possible to monitor ICP more easily and repeatedly in patients with a variety of neurosurgical conditions, thus aiding clinical management and reducing the mortality and morbidity related to neurological diseases.

We have developed a new ultrasonic device to measure ICP waveforms. Although mean ICP is commonly used for ICP monitoring, the analysis of ICP waveforms is also important because the waveforms contain information on intracranial compliance and cerebrovascular tonus, which cannot be estimated from mean ICP [1]. Our technique [8], the principle of which is called pulsed phase-locked loop (PPLL) method, is based upon detecting skull movements which occur with fluctuations in ICP. Although the skull is often assumed to be a rigid container with a constant volume, many researchers [2–5,7] have demonstrated that the skull moves on the order of a few μm in association with changes in ICP. The present study was designed to validate our noninvasive technique for the measurement of ICP waveforms.

Technique

The ultrasound technique [8] we utilized to detect skull pulsation is based upon a modification of the pulsed phase-lock loop design, which makes it possible to measure slight changes in distance between an ultrasound transducer and a reflecting target. Sensitivity of the device is on the order of 0.1 μm. In the typical operation of the PPLL, the instrument transmits a 500 kHz ultrasonic tone burst through the cranium via a transducer placed on the head. The ultrasonic wave passes through the cranial cavity,

reflects off the inner surface of the opposite side of the skull, and is received by the same transducer. The instrument compares the phase of emitted and received waves and alters the frequency of the next stimulus to maintain a 90° phase difference between the output of the device and the received signal. This repetition takes place at intervals of approximately 0.5 msec to 20 ms.

The details of PPLL are described elsewhere [8,9]. Briefly, if path length is changed by Δl, the frequency shift (Δf) of the ultrasound which is made to maintain the 90° phase difference between the output of the device and the received signal can be expressed as $\Delta l/l = -\Delta f/f$ (see Appendix). This is the fundamental PPLL technique. In order to provide continuous monitoring, we modified the PPLL circuit to integrate error signals of the phase shift from normal 90° phase difference (PPLL output). Theoretically, integration of the error signals also correlates with altered path length (Δl).

Methods

Bench Test

A specially constructed aluminum cylinder was used to examine the PPLL output characteristics. Two pressure-resistant tubes were connected to the cylinder filled with saline. The other ends of the two tubes were connected to a plastic syringe and a fiber-optic, transducer-tipped catheter (Camino Laboratories, San Diego) which measures fluid pressure, respectively. An ultrasonic transducer was placed on the top of the cylinder. Pressure pulsations were generated at a frequency of 1 Hz by pumping the syringe while its amplitudes were changed randomly. Changes in distance were calculated from changes in ultrasound frequency.

Cadaver Study

The correlation between the PPLL output and ICP were evaluated in two fresh cadavera (age 85 and 90) which were less than 48 hours postmortem. In supine position, a catheter was inserted to the frontal horn of the right lateral ventricle through a burr hole, and the other end of the catheter was connected to pressure tubing and a plastic syringe. To correlate the PPLL output with ICP directly, a fiber-optic, transducer-tipped catheter was placed in the epidural space through another burr hole. The ultrasound transducer was placed on the temporal area above the ear and fixed with pressure cuff around the head to adjust the surface pressure on the transducer. Pulsatile changes in ICP were generated by infusing saline into the lateral ventricle at a frequency of 1 Hz. In the first experiment (cadaver A), we recorded the PPLL output while generating ICP pulsations and thereafter increased the circumference pressure around the head in steps of 10 mm Hg (0–40 mm Hg) by inflating the pressure cuff. In the second experiment (cadaver B), we recorded the pulsatile PPLL output by infusing saline of different temperatures into the ventricle (4°C and 20°C).

Data Analysis

The amplitudes were calculated based upon the fundamental harmonic of the data using 256 point-fast Fourier transformation (sampling rate: 50 Hz) to avoid distortion caused by other frequency waves.

Results

Bench Test

Our model experiments demonstrated that changes in the PPLL output correlated with changes in the distance to a high degree (Fig. 1). Theoretically, the distance calculated from the ultrasound frequency can be obtained independently of PPLL output. In the results, PPLL output is expressed as:

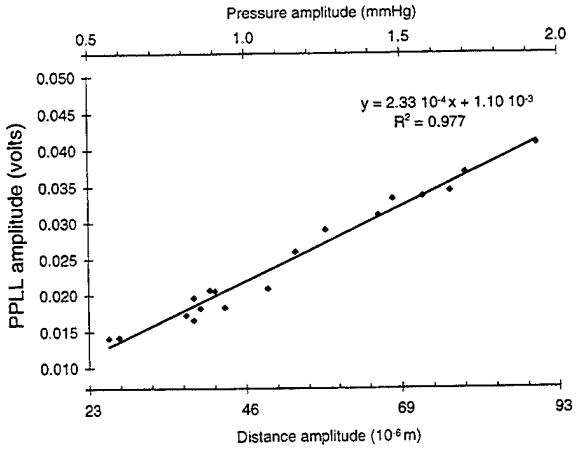

Fig. 1. The relation of the PPLL output to the pressure inside the cylinder and the distance between the transducer and the bottom of the tank is shown, where x = distance (μm) and y = PPLL output (voltage)

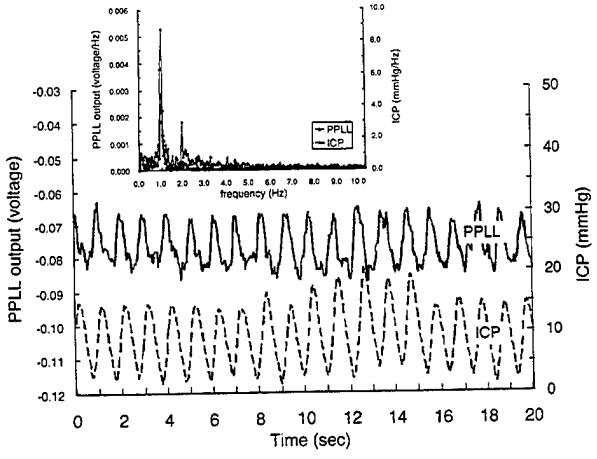

Fig. 2. Typical waveforms in the PPLL output and directly measured ICP are shown as solid and dash lines, respectively. The results of frequency analysis (fast Fourier transformation) are provided in the top inset

$$\Delta \text{int}\ (\text{voltage}) = 2.33 \cdot 10^{-4} \Delta l\ (\mu\text{m}) \qquad (1)$$

Where Δint and Δl are the changes in PPLL outputs and distance, respectively.

Cadaver Study

The PPLL output closely followed the pulsatile component of ICP (Fig. 2). The results of fast Fourier transformation are provided in the top insert, showing the coincidence between the PPLL output and ICP pulse cycles. In the results of the first experiment, the ratio of PPLL amplitude to ICP amplitude significantly decreased along with increased external compression around the head:

$$y = -1.0 \cdot 10^{-5} x + 0.0008,\ R^2 = 0.87\ (p = 0.020)$$

where x = circumferencial compression (mmHg) and y = ratio of PPLL amplitude to ICP amplitude (voltage/mmHg). In the second experiment, the correlation between the PPLL and ICP amplitudes was expressed as the same equation in both saline temperatures:

$$y = 3.0 \cdot 10^{-4} x + 0.0011 \qquad (2)$$

where x = ICP amplitude (mmHg) and y = PPLL amplitude (voltage).

Discussion

The results demonstrate that our PPLL device can clearly detect changes in the integrated phase shifts of the transmitted ultrasound (PPLL outputs) in association with alterations in ICP. As shown in the Appendix, the observed phase shift can be caused by changes in the distance between the transducer and the opposite side of the skull and also by changes in the ultrasound velocity in the cranium. However, we believe that changes in the PPLL output observed in the present cadaveric study represent small but detectable skull movements associated with alterations in ICP.

Infusion of saline into the ventricle could change the temperature inside the cranium, resulting in altered sound velocity. As another possible factor, changes in the density of the brain tissue due to altered ICP could affect ultrasound velocity. In the cadaver study, however, no significant difference was observed in the amplitudes of PPLL when different temperature saline was infused into the ventricle. Also, increased circumference pressure around the head decreased PPLL amplitudes. This observation cannot be explained by changes in ultrasound velocity. This study may be the first report to measure skull movements noninvasively in association with alterations in ICP.

According to the Eq. 2, the ratio of PPLL amplitude to ICP amplitude is expressed as:

$$\Delta \text{int}/\Delta \text{ICP} = 3.0 \cdot 10^{-4} (\text{voltage}/\text{mmHg}) \qquad (3)$$

Using equations 1 (shown in the Results) and 3, the skull elastance, defined as ΔICP/ΔI, is approximately 1.6mmHg/μm (= $2.33 \cdot 10^{-4}/(3.0 \cdot 10^{-4}) \cdot 2$). Heisey and Adams [3] demonstrated that skull elastance in adult cats is 4.5mmHg/μm by invasively measuring the skull movement across the sagittal suture with strain gauge. The difference between our data and theirs might be due to the difference in skull elastance between cat and human. Also, we measured skull movements transversely, while they measured the movement only across the sagittal suture. This difference in the site of measurement may affect changes in the distance obtained.

In conclusion, our technique allows analysis of ICP waveforms noninvasively and will be helpful for understanding intracranial compliance and cerebrovascular tonus in general clinical settings.

Acknowledgements

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Appendix

Changes in wavelength after the frequency shift which maintains a 90° phase difference between the output of the device and the received signal can be expressed as:

$n\Delta\lambda = \Delta l$ ($\Delta\lambda$: changes in wavelength, Δl: changes in distance)

where $n = l/\lambda$ (l: initial distance between a transducer and a target, λ: initial wavelength).

Therefore, $\frac{\Delta\lambda}{\lambda} = \frac{\Delta l}{l}$

Also, $\Delta\lambda = \frac{\partial\lambda}{\partial v}\Delta v + \frac{\partial\lambda}{\partial f}\Delta f$ where Δv is changes in ultrasound velocity, and $f = v/\lambda$.

Solving these equations, we obtain $\frac{\Delta f}{f} = \frac{\Delta v}{v} - \frac{\Delta l}{l}$

If changes in sound velocity are negligible, the above equation is finally expressed as $\frac{\Delta f}{f} = -\frac{\Delta l}{l}$

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POSTURAL EFFECTS ON INTRACRANIAL PRESSURE AS ASSESSED NONINVASIVELY. T. Ueno, R.E. Ballard, L.M. Shuer, J.H. Cantrell, W.T. Yost and A.R. Hargens. NASA Ames Research Center, Gravitational Research Branch, Moffett Field, CA., Stanford Medical Center, CA., and NASA Langley Research Center, VA.
This study was designed to investigate effects of whole body tilting on intracranial compliance and pressure in six healthy volunteers by using a noninvasive ultrasonic device. Subjects were randomly tilted up or down sequentially at 60 degree, 30 degree head-up, supine, and 15 degree head-down position for one minute at each angle. We measured arterial blood pressure with a finger pressure cuff and changes in intracranial distance with an ultrasonic device. The device measures skull movement on the order of micrometer. Our ultrasound technique demonstrates that skull movement is highly correlated (r^2=0.77) with intracranial pressure variations due to cerebral arterial pulsation. The amplitudes of arterial pressure (r^2=0.99) and those of intracranial distance changes (r^2=0.87) associated with one cardiac cycle were inversely correlated with the angle of tilt. The ratio of pulsation amplitudes for intracranial distance over arterial pressure also showed a significant increase as the angle of tilt was lowered (p=0.003). Thus, postural changes alter intracranial compliance in healthy volunteers and intracranial volume-buffering capacity is reduced in head-down position. (This research was supported by NASA grant 199-80-02-05, Department of the Army grant DAMD 17-97-1-7012, and National Research Council Senior Fellowship to TU.)

Ueno T, RE Ballard, LM Shuer, JH Cantrell, WT Yost, and AR Hargens. Postural effects on intracranial pressure as assessed noninvasively. FASEB Journal 12(5):A958 (5550), 1998.

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NON-INVASIVE MEASUREMENT OF PULSATILE INTRACRANIAL PRESSURES USING ULTRASOUND

Toshiaki Ueno[1], Richard E. Ballard[1], Lawrence M. Shuer[2], John H. Cantrell[3], William T. Yost[3], Alan R. Hargens[1]
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Introduction Early detection of elevated intracranial pressure (ICP) will aid clinical decision-making for head trauma, brain tumor and other cerebrovascular diseases. Conventional methods, however, require surgical procedures which take time and are accompanied by increased risk of infection. Accordingly, we have developed and refined a new ultrasound device [1] to measure skull movement which are known to occur in conjunction with altered ICP[2]. The principle of this device is based upon pulse phase locked loop (PPLL), which enables us to detect changes in distance on the order of μm between an ultrasound transducer on one side of the skull and the opposite inner surface of the cranium. The present study was designed to verify this measurement technique in cadavera.

Methods Transcranial distance was increased in steps of 10 mmHg from zero to 50 mmHg by saline infusion into the lateral ventricle of two cadavera. In separate experiments, pulsations of ICP with the amplitudes of zero to 2 mmHg were generated by rhythmic injections of saline using a syringe.

Results When the ICP was stepwise increased from zero to 50 mmHg, transcranial distance increased in proportion with the ICP increase ($y=12x-76$, $r=0.938$), where y is changes in transcranial distance in μm and x is ICP in mmHg. In the data recorded while ICP pulsations were generated, fast Fourier transform analysis demonstrated that cranial pulsations were clearly associated with ICP pulsations.

Summary and Conclusions The results indicate that changes in transcranial distance is linearly correlated with those in ICP, and also that the PPLL device has sufficient sensitivity to detect transcranial pulsations which occur in association with the cardiac cycle. By analyzing the magnitude of cranial pulsations, we may be able to estimate the pressure-volume index in the cranium. As a result, estimates of intracranial compliance may be possible by using the PPLL device. Further studies are necessary in normal subjects and patients. (Supported by NASA and the US Army Medical Research Material Command, and a National Research Council senior fellowship to TU)

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CEREBRAL BLOOD FLOW VELOCITY AND CRANIAL FLUID VOLUME DECREASE DURING +G_Z ACCELERATION

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Kawai, Y. , S.C. Puma, A.R. Hargens, G. Murthy, D. Warkander and C.E.G. Lundgren. Cerebral blood flow velocity and cranial fluid volume decrease during +G_Z acceleration. *J. Grav. Physiol.* 4(3) 31-34, 1997. — Cerebral blood flow (CBF) velocity and cranial fluid volume, which is defined as the total volume of intra- and extracranial fluid, were measured using transcranial Doppler ultrasonography and rheoencephalography, respectively, in humans during graded increase of +G_Z acceleration (onset rate: 0.1 G/s) without straining maneuvers. G_Z acceleration was terminated when subjects' vision decreased to an angle of less than or equal to 60°, which was defined as the physiological end point. In five subjects, mean CBF velocity decreased 48% from a baseline value of 59.4 ± 11.2 cm/s to 31.0 ± 5.6 cm/s ($p<0.01$) with initial loss of peripheral vision at 5.7 ± 0.9 G_Z. On the other hand, systolic CBF velocity did not change significantly during increasing +G_Z acceleration. Cranial impedance, which is proportional to loss of cranial fluid volume, increased by 2.0 ± 0.8 % above the baseline value at the physiological end point ($p<0.05$). Both the decrease of CBF velocity and the increase of cranial impedance correlated significantly with G_Z. These results suggest that +Gz acceleration without straining maneuvers decreases CBF velocity to half normal and probably causes a caudal fluid shift from both intra- and extracranial tissues.

Key words: Gravity-induced loss of consciousness (GLOC), centrifugation, cerebral circulation, transcranial Doppler (TCD)

INTRODUCTION

Hypergravitational forces of 9 G_Z that pilots are exposed to during operation of military aircraft may decrease arterial pressure and fluid content in the head below a level at which adequate cerebral blood flow (CBF) and hydration can be maintained. The most serious consequence of the decrease in CBF is a gravity-induced loss of consciousness (GLOC). In order to avoid GLOC, pilots of high-speed aircraft wear anti-G suits which prevent blood pooling in the lower-body segments (5) and perform straining maneuvers during +G_Z acceleration (9). Straining maneuvers improve +G_Z tolerance by increasing systemic arterial pressure (9). Tripp and Chelette (11) measured cerebral blood flow velocity during +G_Z acceleration with L-1 or M-1 straining maneuvers. The velocity decreased to approximately 75% of control at 6.5 G_Z. However, little information is available with respect to intracranial hemodynamic changes during +G_Z acceleration without straining in humans except that reported by Ossard and coworkers (7) who examined the effects of 0.4 G/s onset of acceleration. The present study was undertaken to investigate cerebral blood flow velocity and cranial fluid volume during relatively-slow onset (0.1 G/s) of +G_Z acceleration without straining.

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METHODS

Subjects:

Five male National Guard pilots (age 37 ± 8 y, height 1.8 ± 0.05 m and weight 89 ± 9.7 kg) participated in the study at State University of New York (SUNY), Buffalo. The protocol for this investigation was approved by the SUNY Institutional Review Board on Human Subjects and Experimentation. Before informed consent was obtained, details and risks of the protocol were fully explained to each subject. Subjects had a current military flight physical examination prior to the study and were in excellent health and not taking any medication. Subjects wore standard flight suit, boots, and helmet, but did not wear an anti-G suit.

Technique:

Cerebral blood flow velocity was monitored using transcranial Doppler (TCD) ultrasonography (1). The right middle cerebral artery was insonated using a pulsed-wave pediatric transducer (Medasonics Inc., Fremont, CA) through the temporal window where the bone is thin. Ultrasonic waves emitted by this transducer have a FDA-approved low frequency (2 MH_Z) and high power, so that the signal can adequately penetrate the dense cranium. The transducer was attached to the subject's head at the window by means of a headband, which included a plastic holder to secure the transducer at a selected angle during the measurement. Sampling depth ranged between 45 and 55 mm. The transducer was connected by cable to the TCD control unit, which was placed at the center of centrifuge arm to avoid signal disturbance due to acceleration. The TCD signals were recorded and stored on VHS video tape, which was the only available method for storing data. There was no noise interference that caused inaccuracies of CBF velocity calculations.

Alterations of cranial fluid volume were determined by rheoencephalography (10). Tetrapolar electrodes were securely placed on the skin of the left temple and behind the right ear to avoid relative movement on the skin. Changes in mean impedance, which reflects the loss of cranial fluid volume, were measured by an impedance cardiograph (Model 400, Instrumentation for Medicine, Greenwich, CT). Impedance calibrations were performed using precision resistors of known values. The frequency of the ICG signal was about 100 KHz.

Gravitational force (G_Z) was measured at heart level by an accelerometer. Cardiac function was monitored by standard three-lead electrocardiography (ECG), and heart rate was calculated from the ECG record.

Protocol:

Hypergravity environment was generated by a human-rated centrifuge located in the SUNY Center for Research in Special Environments, Buffalo, NY. To examine the reproducibility of Gz tolerance, subjects were seated in the centrifuge capsule and exposed to five centrifugation runs with five minute interval between runs; One of the subject was exposed to only three runs. Acceleration profiles included a warm-up exposure of 1.2 G_Z for 10 seconds and progressive increase of $+G_Z$ force with onset rate of 0.1 G/s. As the velocity increased, the capsule was automatically rotated so as to continuously align the subject's z axis with the axis of the G force. The acceleration was terminated when the subject's vision decreased to an angle of less than or equal to 60° indicated on a light bar at front of the subject, which was defined as the physiological end point. Subjects were asked to relax as much as possible during centrifugation.

Data analysis:

The following parameters were quantified from the TCD waveform signal: 1) mean CBF velocity (V_{mean}) calculated by mean envelope method (1) and 2) peak CBF velocity (V_S) which is the maximum systolic velocity. $+G_Z$ tolerance was defined as G_Z level at the previously-defined physiological end-point.

Experimental values are reported as mean ± SE. Because of technical difficulties, good signals for impedance could not be obtained in one subject. In Figure 1, data were averaged over five subjects at $1G_Z$, $1.2G_Z$, $2G_Z$, $3G_Z$, $4G_Z$, $5G_Z$, and the physiological end point in the final run. Impedance results reflect data from 4 subjects only. Since the end point varied between subjects, the values at the end point have horizontal error bars. Results were analyzed using analysis of variance for repeated measures, t-test, and linear regression. The difference in means was considered significant when $p < 0.05$.

RESULTS

The G_Z force at the physiological end point was compared between 5 runs without straining in four subjects. The G_Z tolerance in the first run (6.5 ± 0.8 G_Z) was slightly higher than in the other runs (range 5.7-5.9 G_Z).

Figure 1 indicates changes in CBF velocity and impedance during centrifugation of the final run. Mean CBF velocity decreased 48% from a baseline of 59.4 ± 11.2 cm/s during 1 G_Z to 31.0 ± 5.6 cm/s ($p<0.01$) at the physiological end point of 5.7 ± 0.9 G_Z. The highest G_Z level shown in Figure 1 varies because the G_Z tolerance varied between subjects. Peak CBF velocity at 1 G_Z was 96.4 ± 14.8 cm/s and did not change significantly during centrifugation.

At higher G_Z forces, the TCD signal was manifested as a two-peak waveform, suggesting a marked decrease of CBF velocity during diastole (Fig. 2). Impedance increased by 2.0 ± 0.8 % of baseline value (98.4 ± 4.8 W) at the end of centrifugation ($p<0.05$) (Fig. 1). Heart rate increased significantly from 73 ± 11 beats/min at 1 G_Z to 117 ± 9 at the end point. Significant correlations were observed between altered mean CBF velocity ($R=0.89$, $p<0.001$) and impedance ($R=0.60$, $p<0.01$) as a function of G_Z force.

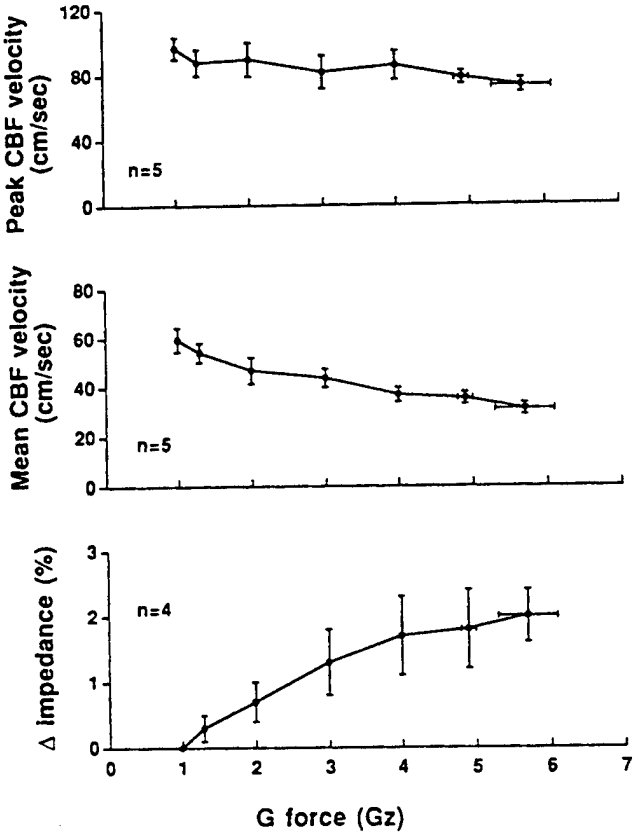

Figure 1. Peak and mean CBF velocity, and percent change in impedance during $+G_z$ acceleration without straining. Vertical and horizontal bars indicate standard error of the mean.

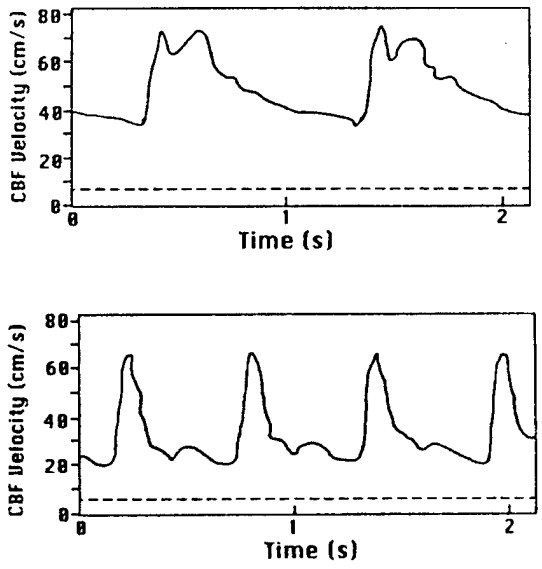

Figure 2. A schematic waveform of TCD signal at 1 G_z (upper-panel) and during presyncopal +Gz acceleration (lower panel).

DISCUSSION

Mean CBF velocity gradually decreased as G_z force increased during relatively-slow onset centrifugation without straining. Although arterial blood pressure was not monitored in our study, the decrease in mean CBF velocity may be attributed to reduced perfusion pressure in the brain due to hydrostatic effect of headward acceleration. Wood and co-workers (13) calculated mean arterial pressure at the base of brain to be zero at +5 G_z, while the pressure at heart level was 120 mmHg. Rositano (8) measured arterial blood pressure at eye level using a miniature strain gauge transducer and found that the mean arterial pressure decreased to 20 mmHg at about +3.5 G_z of gradual onset (0.1 G_z/sec) centrifugation. The cerebral venous pressure falls to negative 20 - 60 mmHg during exposure to (relatively) rapid onset of + G_z, but the magnitude of the venous pressure fall is far less when the onset of acceleration is gradual (4). Thus, high G_z acceleration with slow onset may decrease cerebral perfusion pressure below the normal autoregulatory range of 60 to 140 mmHg.

Our data suggest that decreased mean CBF velocity represents a reduction of velocity during diastole, because peak CBF velocity during systole remained unchanged. This was also supported by the change of the velocity waveform (Fig. 2). The second peak in the waveform represents the velocity during diastole because the notch is due to closure of aortic valve, and it was much lower than the first peak. Assuming that the diastolic pressure at heart level is 80 mmHg and the distance between heart and brain is 35 cm, the diastolic pressure at brain level would be below zero when the G_z force is greater than +3 G_z. Theoretically one expects that diastolic CBF velocity decreases considerably during $+G_z$ acceleration and in fact, this is what was found in this study. Hemodynamic changes induced by $+G_z$ acceleration are reasonably expected to cause some compensatory mechanisms such as baroreceptor reflex and central nervous system ischemic response. However, such mechanisms do not seem to be strong enough to maintain diastolic CBF velocity in a subject exposed to high G_z. On the other hand, the stable peak CBF velocity found in this study (Fig. 1) suggests that such compensatory mechanisms, in addition to the autoregulation, maintain adequate cerebral blood flow during G_z-induced hypotension. One other possible explanation can be that a reduction of intracranial pressure in turn may increase brain perfusion pressure. The elevated impedance (Fig. 1) indicates decreased cranial fluid volume (10) a part of which presumably resulted from reduction of

intracranial fluid (venous blood and cerebrospinal fluid). Exposure to simulated microgravity causes a cephalad fluid shift which in turn elevates intracranial pressure in humans (6). Thus, it is reasonable to infer that downward fluid shift due to $+G_Z$ acceleration decreases intracranial pressure.

Our results indicate that mean CBF velocity at +5.7 G_Z without straining was almost 50% lower than baseline velocity. This decrease of CBF velocity is greater than that reported by Tripp and Chelette (11). They found that mean CBF velocity decreased by 20% of baseline velocity during +5.0 G_Z with straining maneuvers and leveled off during +5.5 and +6.0 G_Z acceleration. The straining maneuver elevates intrathoracic pressure and systemic arterial pressure (9) which in turn increases blood flow velocity in the temporal artery (8). These findings suggest that straining also increases mean CBF velocity which improves G_Z tolerance. CBF velocity during centrifugation was also measured by Werchan and Forster who demonstrated that combination of straining and anti-G suits counteracts Gz-induced reduction of CBF velocity more effectively than straining alone (12).

The increase in transcranial impedance during increased G_Z is noteworthy. Reduction in electrolyte volume between the electrodes, commensurate with altered impedance, can be attributed to a reduction in extracranial (skin blood and fluid) and intracranial (cerebral blood, brain tissue fluid, and cerebrospinal fluid) fluid volume. We can not distinguish whether the reduction of fluid volume is of intracranial or extracranial origin. It most likely reflects a loss from both fluid compartments. Adams and coworkers (2,3), for example, showed that injection of artificial cerebrospinal fluid into the lateral ventricle caused lateral expansion of the parietal bones at the sagittal suture along with corresponding increase in intracranial pressure. Thus, intracranial fluid volume was likely decreased in our studies of G-load. In conclusion, our findings suggest that $+G_Z$ acceleration greatly reduces cerebral blood flow velocity and shifts fluid caudally from intra- and extracranial tissues.

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Development of a noninvasive technique for the measurement of intracranial pressure

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Introduction

Intracranial pressure (ICP) dynamics are important for understanding adjustments to altered gravity. Previous flight observations document significant facial edema during exposure to microgravity, which suggests that ICP is elevated during microgravity. However, there are no experimental results obtained during space flight, primarily due to the invasiveness of currently-available techniques. We have developed and refined a noninvasive technique to measure intracranial pressure noninvasively. The technique is based upon detecting skull movements of a few m in association with altered intracranial pressure [1, 2]. We reported that the PPLL technique has enough sensitivity to detect changes in cranial distance associated with the pulsation of ICP in cadavera [3]. In normal operations, however, we place a transducer on the scalp. Thus, we cannot rule out the possibility that the PPLL technique picks up cutaneous pulsation.

The purpose of the present study was therefore to show that the PPLL technique has enough sensitivity to detect changes in cranial distance associated with cardiac cycles *in vivo*.

Methods

Technique: The ultrasound technique [4] we utilized to detect skull pulsation is based upon a modification of the pulsed phase-lock loop (PPLL) design, which makes it possible to measure slight changes in distance between an ultrasound transducer and a reflecting target. In the typical operation of the PPLL, the instrument transmits a 500 kHz ultrasonic tone burst through the cranium via a transducer placed on the head. The ultrasonic wave passes through the cranial cavity, reflects off the inner surface of the opposite side of the skull, and is received by the same transducer. The instrument compares the phase of emitted and received waves and alters the frequency of the next stimulus to maintain a 90° phase difference between the output of the device and the received signal. This repetition takes place at intervals of approximately 0.5 msec to 20 msec.

Measurement: All measurements were conducted at the Stanford Medical Center. Three patients who underwent craniotomy with no previous neurosurgical history participated in this study. After obtaining informed written consent, we set up our measurement system in an operating room. Patients underwent endotracheal general anesthesia. After the skull surface was exposed, a surgeon placed a gas-sterilized transducer directly on the skull in the temporal area. Measurements were performed for three minutes. Arterial blood pressure measured at the brachial artery was also recorded simultaneously. All data were recorded at the sampling rate of 50 Hz.

Results

Figure 1 shows the waveforms of the PPLL output and arterial blood pressure, representing data from one cardiac cycle. It appears that a phase delay exists in the peaks between the PPLL output and arterial blood pressure. This can be explained by the difference in distance from the heart to the head and the brachial artery. Data in two other patients were quite similar to the waveforms shown in Figure 1.

Discussion

The results indicate that the PPLL output is clearly associated with the cardiac cycle. Because we placed a transducer directly on the skull in the present study, there is no possibility that the pulsation of the PPLL output was generated by cutaneous pulsation. We may conclude that the PPLL technique has enough sensitivity to detect pulsatile components of ICP through changes in cranial distance.

In this study, we were not able to measure ICP by the standard invasive method. Future studies are therefore necessary to show the direct correlation between invasively measured ICP and PPLL outputs. We are currently conducting a clinical study in patients whose ICP is directly measured by the standard invasive technique.

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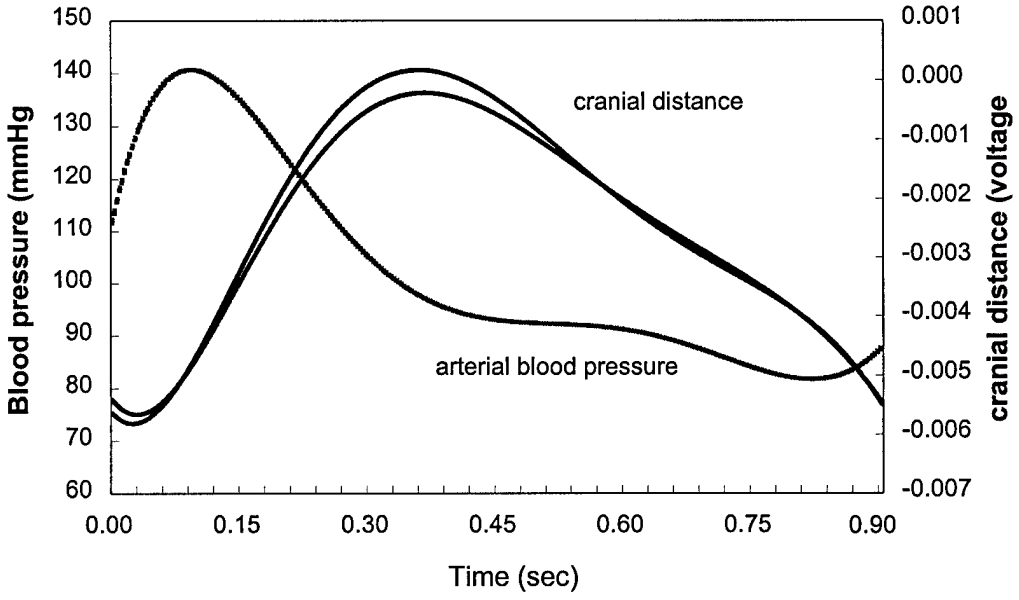


Figure 1 Cranial distance measured by PPLL technique and arterial blood pressure at the brachial artery. Two waveforms of cranial distance (PPLL output) recorded during two separate periods are shown.

Ultrasonic Measurement of Intracranial Pressure Waveforms

Masayuki Matsuyama, Toshiaki Ueno, Brandon Macias, Robert A Pedowitz, Sonya Waters, William T. Yost, John H. Cantrell, and Alan R. Hargens

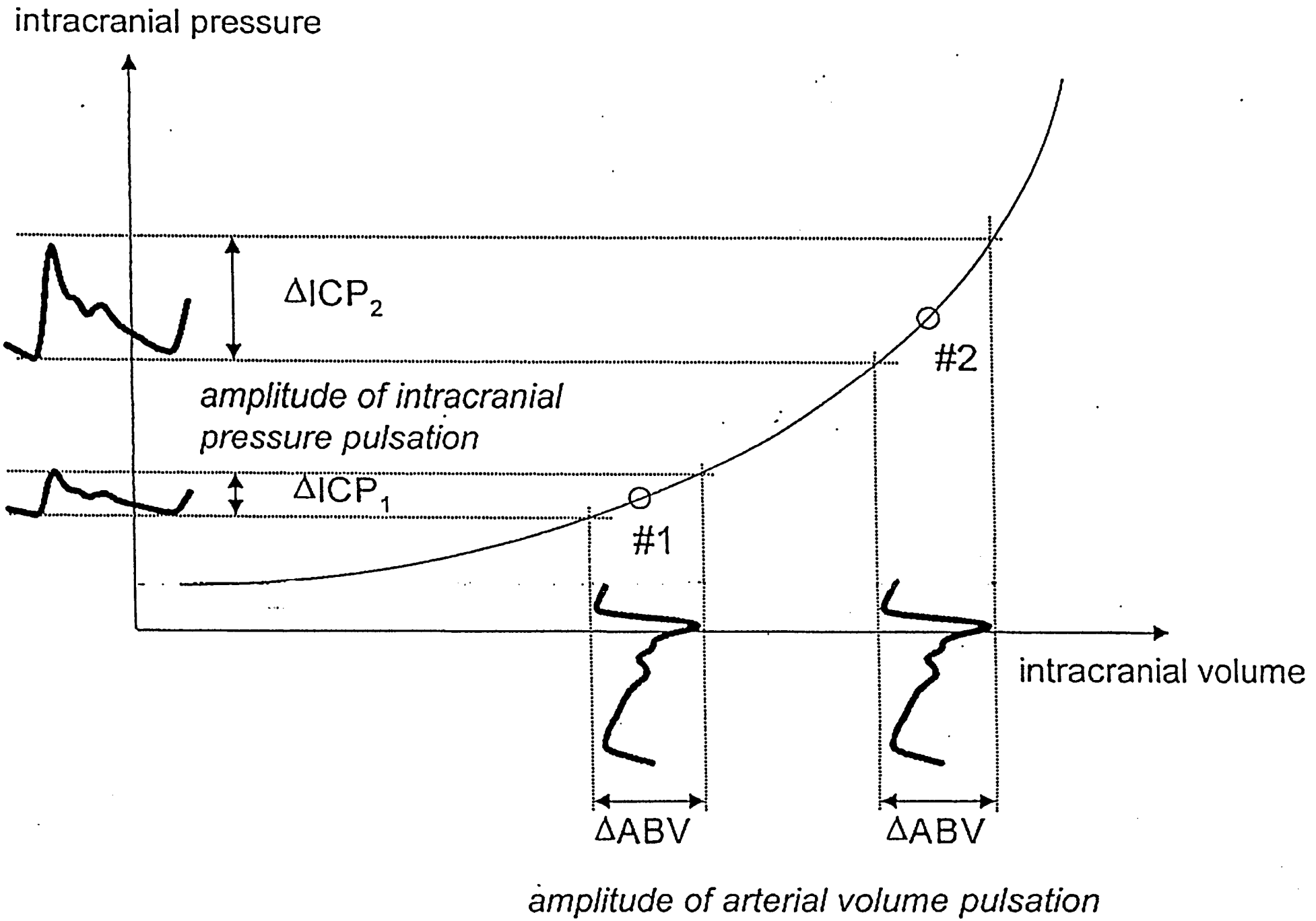
Control of intracranial pressure (ICP) is very important in patients with head trauma, cerebrovascular disease, brain tumor, and hydrocephalus. Several invasive methods are used for ICP measurement: 1) cerebrospinal fluid pressure measurement from lumbar puncture, 2) intraventricular pressure measurement using a needle, and 3) epidural catheter insertion through the cranium. Generally speaking, ICP is a static pressure. On the other hand, we have developed a noninvasive technique to monitor ICP pulsation in which blood pressure waves and respiratory movements are added onto the static ICP. ICP pulse waves are mainly derived from blood pressure waves which are modified by intracranial compliance. ICP dynamics are also important for understanding adjustments to altered gravity. ICP may increase during microgravity due to a blood and tissue fluid shift to the head. As widely observed in clinical settings, elevated ICP causes headache, nausea, and vomiting, symptoms which are similar to those of space adaptation syndrome.

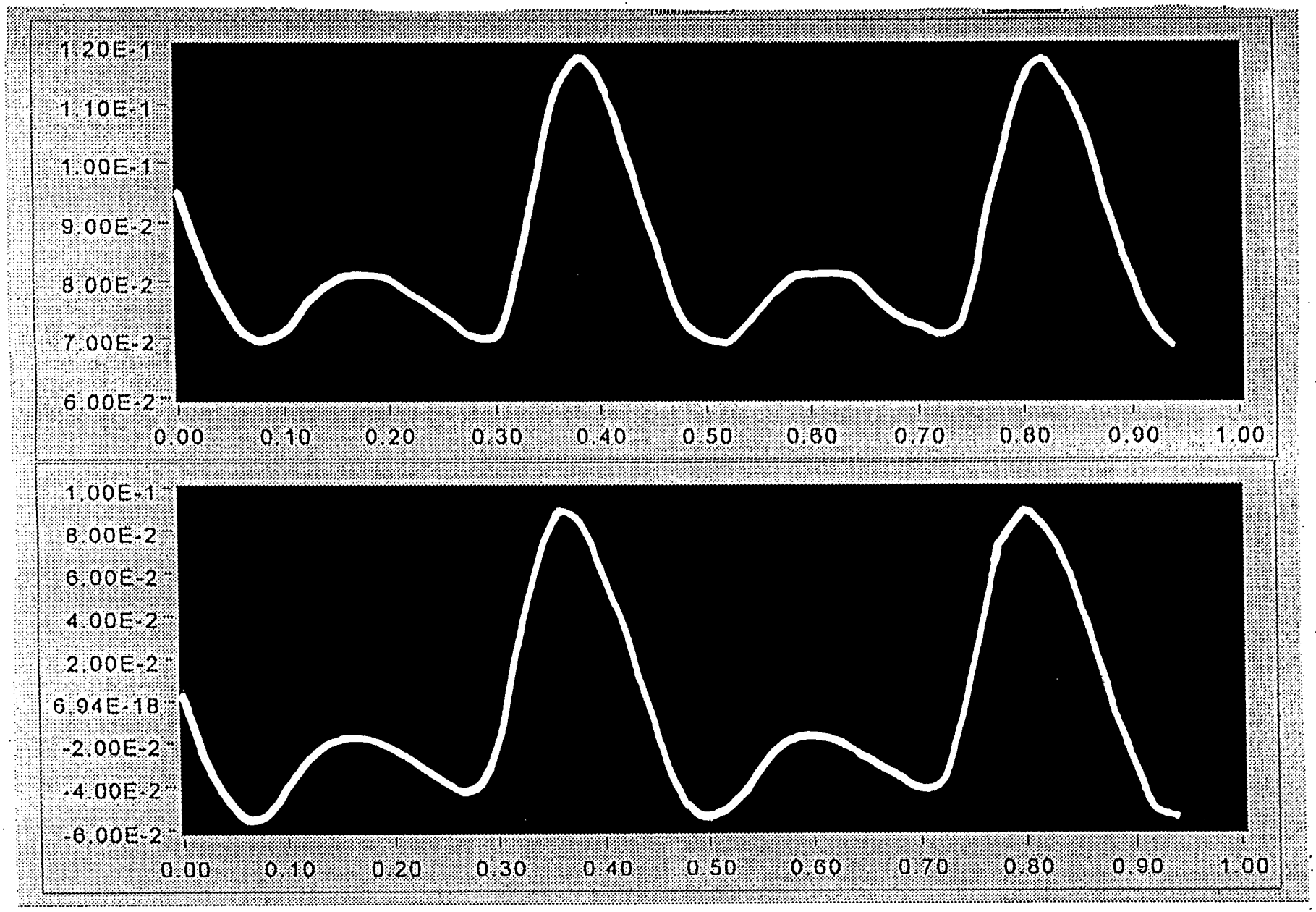
An ultrasonic device which measures changes of intracranial distance noninvasively using a Pulse Phase Lock Loop (PPLL) technique was initially patented by Drs. Yost and Cantrell at Langley Research Center and refined for patient studies by staff at Ames Research Center. The skull moves on the order of a few micrometers in association with ICP pulsation due to arterial pressure pulsation within the brain. Our ultrasonic device records ICP waveforms noninvasively from skull movements, and enables us to evaluate ICP dynamics noninvasively by analyzing pulsatile components of these ICP waveforms. Amplitudes of pulsatile components of ICP yield information on intracranial

compliance, representing the change in volume of any intracranial component (brain, blood or cerebrospinal fluid) with ICP change. Clinically, intracranial compliance is important to monitor because it represents the volume-buffering capacity of the intracranial tissues and fluids. In addition, because the intracranial volume-pressure curve is generally exponential, an inverse relationship exists between intracranial compliance and pressure. Thus, mean ICP levels can be estimated from pulsatile components of ICP waveforms (Fig. 1).

We have reported that pulsatile changes of intracranial distance are associated with a cardiac cycle. In the present project, new data were obtained from patients in whom PPLL measurements were compared to direct invasive measurements of ICP at the UCSD Trauma Center. There was good correlation between directly-measured ICP waveforms and waveforms from our ultrasonic device (Fig. 2). When ICP was elevated, the amplitude of distance waves from our ultrasonic device was also increased. These results indicate that changes in ICP on the order of a few mmHg may be detectable by our noninvasive technique.(This research was supported by NASA grant 199-80-02-05 and Department of the Army grant DAMD 17-97-1-7-7012.)

(Fig. 1) Mean ICP can be estimated from the increase of PPLL pulsatile amplitudes as ICP increases in the patient. The horizontal axis represents volume of all intracranial components (brain tissue, blood, and cerebrospinal fluid).
(Fig. 2) Comparison of pulsatile amplitude and frequency of direct ICP waveforms (above) and noninvasive PPLL distance waveforms (below).


intracranial pressure
ΔICP2
amplitude of intracranial pressure pulsation
ΔICP1
#2
#1
intracranial volume
ΔABV
ΔABV
amplitude of arterial volume pulsation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